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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,251	10/20/2006	Luca Gianni	13566.105020	7104

65989 7590 01/08/2010

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EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
01/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/579,251	GIANNI ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 pgs / 12/3/2008, 10/02/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 2 Oct 2009.

This application is the national stage entry of PCT/GB04/50025, filed 12 Nov 2004; and claims benefit of foreign priority document UNITED KINGDOM 0326486.8, filed 14 Nov 2003. The foreign priority document is in English.

Claims 1, 3-10 and 12-15 are pending.

Information Disclosure Statement

The IDS previously filed 12/3/2008 has been considered.

The IDS filed 10/02/2009 has been considered.

The following grounds of rejection are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended Claims 1, 3-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. (WIPO publication WO 02/36135, published 10 May 2002, of record), hereafter WIPO '135, in view of van Kesteren et al. (Clinical Cancer Research, 2000, 6, p4725-4732, cited in PTO-892) and in view of Takahashi et al. (Clinical Cancer Research, 2001, 7, p3251-3257, provided by Applicant in IDS filed 12 May 2006), hereafter "Takahashi et al. 2001", and further in view of Dorr et al. (Cancer Chemotherapy Handbook, 1994, Appleton & Lange, 2nd ed, p395-416, of record).

WIPO '135 discloses the method of combination therapy of ET-743 and doxorubicin to treat the cancer sarcoma (page 2, lines 26-29), specifically envisioning treating a human (page 4, lines 11-12). WIPO '135 discloses the drugs provided as a separate composition for administration at different times (page 1, lines 12-13). WIPO '135 discloses administering ET-743 after administering doxorubicin (page 21, lines 13-14), which is to say administering doxorubicin prior to the administration of ET-743. WIPO '135 discloses administration of the compounds by intravenous infusion, with infusion times of up to 24 hours and 2-6 hours preferred (page 4, lines 25-26). WIPO '135 discloses infusions carried out at suitable intervals of 2 to 4 weeks (page 5, lines 2-

3). WIPO '135 discloses the correct dosage of the compounds will vary according to the particular formulation, mode of application, *situs*, host, and tumor being treated (page 5, lines 6-10).

WIPO '135 does not specifically disclose ET-743 administered with a dose range between 0.6 mg/m^2 and 0.75 mg/m^2 and doxorubicin administered with a dose of about 60 mg/m^2 or about 50 mg/m^2 (instant claim 1). WIPO '135 does not specifically disclose the infusion of doxorubicin carried out once every 21 days (instant claim 9). WIPO '135 does not specifically disclose the method wherein the infusion of doxorubicin is carried out on day 1 and the infusion of ET-743 on days 1 and 8, every 21 days (instant claim 10).

van Kesteren et al. teaches ET-743 administered as a 24 hr i.v. infusion every 3 weeks to a human patient with dosage escalation (page 4726, right column, paragraph 5). van Kesteren et al. teaches ET-743 administered at the dosage 400 to 900 μg/m^2, or 0.4 to 0.9 mg/m^2, results in an increase in plasma concentration that is a predictable trend to one of skill in the art (page 4728, figure 3). van Kesteren et al. teaches ET-743 administered at the specific dosage 600 μg/m^2, or 0.6 mg/m^2, administered every 21 days during multiple courses (page 4728, right column, section RESULTS). van Kesteren et al. teaches it is known in the art that the dosage for a human in terms of μg/m^2 or mg/m^2 can be safely applied at higher dosages than in the mouse model (spanning page 4731, right column, paragraph 4 at bottom and page 4732, left column, paragraph 1 at top).

Takahashi et al. 2001 teaches the effect of ET-743 and doxorubicin is dependent on the sequence of administration of ET-743 and doxorubicin (page 3251, abstract). Takahashi et al. teaches the treatment protocol of ET-743 and doxorubicin administered at a constant molar ratio of 1 ET-743 : 100 doxorubicin (page 3252, left column, Figure 1 at middle of page). Takahashi et al. 2001 teaches a synergistically additive effect of ET-743 followed by doxorubicin after 24 hrs and a synergistically antagonistic effect of doxorubicin followed by ET-743 after 24 hrs are known in the art (page 3254, right column, paragraphs 1-4). Takahashi et al. 2001 teaches a synergistically additive effect of ET-743 and doxorubicin concomitantly (spanning page 3256, left column, paragraph 4 and right column, paragraph 1), which broadly interpreted is the administration of one agent immediately followed by the other agent.

Dorr et al. teaches dosing guidelines for doxorubicin of 60-75 mg/m^2 administered every 3 weeks (page 399, table on lines 38-45), or 21 days. Compared to a dose of up to 120 mg/m^2 (page 399, left column, lines 10-13), a dose of 60 mg/m^2 is about 50 mg/m^2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine WIPO '135 in view of van Kesteren et al. and in view of Takahashi et al. and further in view of Dorr et al. WIPO '135 teaches the method of combination therapy of ET-743 and doxorubicin to treat the cancer sarcoma in a human. One of ordinary skill in the art would have looked to the prior art van Kesteren et al. for dosage of ET-743 administered as an i.v. infusion every 3 weeks to a human patient to treat the cancer sarcoma and the prior art Takahashi et al. 2001 for the teaches the treatment

protocol of ET-743 and doxorubicin administered at a constant molar ratio of 1 ET-743 : 100 doxorubicin concomitantly to treat sarcoma cells. One of ordinary skill in the art would have a reasonable expectation of success in combining WIPO '135 with the dosage taught by in view of van Kesteren et al. and in view of Takahashi et al. because van Kesteren et al. teaches that dosage is safe in a human and Dorr et al. teaches that dosage of doxorubicin and administration every 3 weeks is safe in a human. WIPO '135 discloses the correct dosage of the compounds will vary according to the particular formulation, mode of application, *situs*, host, and tumor being treated (page 5, lines 6-10). It would have been routine experimentation for one of ordinary skill in the art at the time of the invention to optimize dosage of the compounds to result in the method wherein the infusion of doxorubicin is carried out on day 1 and the infusion of ET-743 on days 1 and 8, every 21 days.

Response to Applicant's Remarks:

Applicant's Remarks, filed 2 Oct 2009, have been fully considered and not found persuasive.

Applicant's clarification of antagonistic effects, drawn to the interaction of drugs affecting the effect of the drugs, and adverse effects, drawn to the appearance of effects in the patient, as distinct terms of art is acknowledged. Applicant's remarks regarding unexpected results and the adverse effect of dose-limiting toxicity are addressed below.

Regarding van Kesteren and maximum tolerated dosage (MTD), Applicant remarks that van Kesteren does not lead a person skilled in the art to conclude that the dosage for a human in terms of mcg/m^2 can be safely applied at higher dosages than in

the mouse model. However, at bottom of page 8 Applicant notes that van Kesteren teaches the LD10 (or MTD) for mice is 600 mcg/m^2 and at top of page 9 Applicant acknowledges that van Kesteren teaches a dosage escalation study with a MTD of 1800 mcg/m^2 and recommended dosage of 1500 mcg/m^2. As an MTD of 1800 mcg/m^2 in the humans is a higher dosage than 600 mcg/m^2 in the mouse model, support for the Examiner's position regarding the conclusions made by one of ordinary skill in the art is found in van Kesteren.

With regard to Takahasi describing *in vitro* experiments, MPEP 2143.02 I. provides "The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (Claims directed to a method of treating depression with amitriptyline (or nontoxic salts thereof) were rejected as *prima facie* obvious over prior art disclosures that amitriptyline is a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess antidepressive properties, in view of prior art suggesting the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement and because a research paper comparing the pharmacological properties of these two compounds suggested clinical testing of amitriptyline as an antidepressant. The court sustained the rejection, finding that the teachings of the prior art provide a sufficient basis for a reasonable expectation of success.)" Meco (Cancer Chemother Pharmacol, 2003, provided by Applicant in IDS mailed 13 Nov 2007) provides evidence

of the level of ordinary skill in the art with regard to the predictable expectation of *in vivo* activity from the *in vitro* experiments of Takahasi in the specific field of co-administration of ET-743 and doxorubicin.

With regard to evidence of the level of skill in the art disclosed by Meco and the teaching of van Kesteren, Applicant notes that Newell and the draft guidance from the FDA acknowledge the distinction between data regarding mice and data regarding humans. Applicant notes that there is a high variability between different anticancer drugs. However, van Kesteren discloses data specific to ET-743 with regard to MTD in humans and MTD in mice, not an extrapolation based on different anticancer drugs. Therefore one of ordinary skill in the art would reasonably expect that extrapolation of data specific to ET-743 in humans and in mice based on the teaching of van Kesteren is predictable. It is noted that guidance for selecting the ratio of ET-743 to doxorubicin is taught by Takahasi.

With regards to the evidence showing anti-tumor activity without dose-limiting toxicity, Applicant provides factual evidence such as in Sarosy et al. (provided by Applicant in IDS mailed 3 Dec 2008) regarding alpha2-interferon and doxorubicin, in Boranic et al. (provided by Applicant in IDS mailed 3 Dec 2008) regarding doxorubicin with vincristine, in Chabner et al. (provided by Applicant in IDS mailed 15 Jan 2009) regarding trastuzumab with doxorubicin/cyclophosphamide, and in Perotti et al. (provided by Applicant in IDS mailed 15 Jan 2009) regarding anthracycline-taxane combinations showing evidence of combinations with doxorubicin resulting in undesired toxicity. While Applicant's evidence is directed to the state of the art with regard to

combinations with doxorubicin in general, Meco teaches that ET-743 and doxorubicin did not show any significant pharmacokinetic interaction in mice such that the combination excludes pharmacokinetic related increase in toxicity, which Meco contrasts to the combination of cyclosporin and doxorubicin wherein doxorubicin levels are increased with possible toxicological implications (Meco, page 137, left column, paragraph 3). Meco teaches this lack of pharmacokinetic interaction between ET-743 and doxorubicin is observed in humans as well as in mice (page 137, right column, paragraph 2). Therefore this result of the specific combination of ET-743 and doxorubicin not showing a pharmacokinetic related increase in toxicity is expected based on evidence of the state of the art at the time of the invention provided by Meco.

This rejection is maintained and made FINAL.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Amended Claims 1 and 3-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 19-20 of commonly assigned copending Application No. 11/577,790.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-9 and 19-20 of copending Application No. 11/577,790 are drawn to a method of treating cancer in a human comprising administering ET-743 and a Pegylated Liposomal form of the anthracycline Doxorubicin. Instant claims 1 and 3-9 are drawn to the method of treating cancer in a human comprising administering ET-743 and doxorubicin. The instant specification discloses one non-limiting embodiment wherein the doxorubicin does not take the form of doxorubicin in the Pegylated Liposomal form (page 8, lines 8-10). However, this disclosure leads one to immediately envision the opposite, the embodiment wherein the doxorubicin does take the form of doxorubicin in the Pegylated Liposomal form. Claims 2 and 3 recites the limitation of instant claim 3. Claim 4 recites the limitation of instant claim 4. Claim 5 recites the limitation of instant claim 5. Claim 6 obviates the limitation of instant claim 6. Claim 7 obviates instant claim 7. Claim 8 obviates instant claims 8 and 9. A dosage of 0.6 mg/m^2 or 0.75 mg/m^2 encompassed within claim 9 of copending Application No. 11/577,790 is rendered obvious by the disclosure at page 14, table 5a of the specification of copending Application No. 11/577,790.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's Remarks:

Applicant's Remarks, filed 2 Oct 2009, have been fully considered and not found persuasive.

As this is not the only remaining grounds of rejection, it is proper to maintain this provisional obviousness-type double patenting rejection.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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